ORIGINAL CONTRIBUTION

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Hepatitis C virus induces nasal epithelial erosion and sub-epithelial rhinitis*

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SUMMARY

Background: *Hepatitis C virus (HCV) affects extra-hepatic organs, but its effect on the nose is poorly defined.*

Objectives: *To investigate the histological changes in nasal tissue induced by HCV and whether the nasal mucosa harbors the virus for extrahepatic replication.*

Study Design: *We investigated nasal biopsies from 20 patients with HCV infection, and from 10 control subjects. All biopsies were subjected to real time polymerase chain reaction (RT-PCR) as well as histology.*

Results: *Our analyses showed that 60% of HCV positive samples showed nasal epithelial erosion, 95% showed subepithelial non-specific inflammation and/or fibrosis, while only 5% showed normal histology. However, none of the twenty PCR samples showed the presence of HCV nucleic acids sequences in the nasal tissues. On the other hand, all control subjects had normal histology and the absence of the viral m-RNA in the PCR (100%).*

Conclusions: *HCV induces histopathological rhinitis with nasal epithelial erosion. However, it does not seem that the nasal tissue harbors the virus.*

Key words: HCV, nasal epithelial erosion, epistaxis, non-specific rhinitis

INTRODUCTION

Hepatitis C virus extra-hepatic manifestations (EHM) are largely reported and these include mixed cryoglobulin and its vasculitic manifestations, the chronic fatigue syndrome, cutaneous diseases and lichen planus, the sicca syndrome, the non-insulin-dependent diabetes mellitus, malignant B cell proliferations, mainly the Hepatis C Virus-related splenic lymphoma with villous lymphocytes and the production of auto-antibodies as well as pulmonary manifestations [1-9]. Further support to HCV induced autoimmunity could be deduced from the observation that HCV infects peripheral blood mononuclear cells [10].

In the head and neck region thyroid disease is commonly seen in people with HCV. Correlation between HCV and lymphocytic sialoadenitis, similar to sialoadenitis associated with idiopathic Sjögren syndrome has been also described [6], but nasal EHM of HCV is poorly defined.

Despite hepatocytes being the major site of infection, there is a growing body of evidence to suggest that HCV can replicate efficiently in extrahepatic tissues and cell types [11]. Furthermore, the potential role of body fluids in virus transmission has been investigated and showed HCV RNA detection in 76.5% (39/51) of the sera and in 9.8% (5/51) of the tear fluid samples from 51 patients of chronic hepatitis C [5]. Other studies had also demonstrated a positive reaction in HCV-RNA PCR from plasma, tear fluid and eye swabs but not from nasal and pharyngeal swabs [12,13].

The upper and lower airways are considered to be linked, as signified by the concept of "united airways". While pulmonary manifestations such as reduction of forced vital capacity, forced expiratory volume in first second/forced vital capacity and forced expiratory volume in first second of chronic hepatitis C is documented [9], little is known about the effect of HCV on the nasal tissue.

In our clinical experience we see substantial number of patients with HCV who presented with mild to moderate epistaxis that required several cauterizations, despite normal coagulation profile. Nonetheless, no single report in the English literature to our best knowledge demonstrated increased incidence of epistaxis in HCV patients with normal liver function tests and coagulation profile. To further look into the real incidence of epistaxis in this group of patients, we first performed a preliminary study, in the form of questionnaires that was supplemented by objective liver function tests and coagulation profile (Tables 1 and 2). This confirmed an increased and sig-

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nificant rate of epistaxis in this group of patients, with increased but non-significant rate of non-specific rhinitis symptoms when compared to the control group.

Accordingly we speculated that the significant increased rate of epistaxis seen in HCV patients with normal coagulation profile might be due to nasal erosion and/or vasculitis. Herein, we report the first evidence of the presence of nasal epithelial erosion and subepithelial non-specific inflammation with mild to moderate fibrosis without the presence of the virus in the nasal tissue in patients with HCV infection.

MATERIALS AND METHODS

Subjects

After obtaining their consent and the approval of the scientific committee, a total of 130 subjects participated in the current study. One hundred subjects participated in questionnaires asking about epistaxis, rhinitis symptoms and smoking. They were divided into two groups as follows: a group of 50 control subjects who were recruited from our OPD that presented with complaints other than nasal symptoms, and were confirmed not to have signs of rhinitis by physical examination. Liver function tests, coagulation profile and serum HCV antibody titer were done for them to ensure normal liver status. The other group consisted of 50 patients with HCV infection having normal liver function tests and coagulation profile. They were recruited from the hepatology department.

Another thirty volunteers participated for the histopathology and RT-PCR investigations. Ten control subjects (4M:6F) with mean age of 43.2 who were proved not to be infected with HCV by having negative HCV antibody titer in their sera, and were recruited from our OPD as otology patients going for aural surgery. The other 20 patients (8M:12F) with mean age of 45.5 were recruited from the hepatology department of our University. They were selected being child's classification (A) with proven HCV infection diagnosed by liver PCR and serum antibodies, and had normal liver enzymes levels and coagulation profile at the time of the study. None of the 20 patients received interferon therapy prior to the study. All 30 volunteers had negative prick skin test to common aeroallergens.

Collection of samples

Five ml of blood were obtained by venopuncture for detection of HCV-antibody. A lentil sized nasal mucosa was collected on RNases free water, and kept in -80°C till homogenized prior to RNA extraction, and another in 10% formaline for histological study, after obtaining all volunteers consent and the medical approval of our research committee. In the control group the samples were collected during aural surgical procedures while in the patients group, the sample was collected in the clinic under local anesthesia.

Virological studies

Detection of HCV-antibody in serum was done for all 30 volunteers using a solid phase (ELISA) using a kit purchased from (ADALTIS ITALIA S.P.A.). Quantitative detection of HCV-antigen in tissue was done by HCV-RNA extraction from mucosal tissues utilizing quiagen RNA viral nucleic acid (Qiagen Germany), according to the instruction of the manufacture.

HCV-RNA was amplified in the study group using real time PCR in one step (Robostreen-Germany); the cDNA was first generated using reversed primer (HCV-R2: CGGGTTGATCCAAGAAAGGA). The cDNA was then used as a template for 40 cycles of real time PCR with specific primers and probes; Forward primer (HCV-F2: GAGTGTTGTGCAGCCTCCA) and specific probe (HCV-FB2; FAM-CCTCCCGGGAGAGCCATAGTG-TAMRA) purchased from (BIO-TEZ, Berlin-Buch, Germany). The reaction mixture conditions: Buffer 1x TAMRA-FAM dye and ROX reference dye, 3.5 mmol Mn-acetate solution, 0.3 mmol dNTPs, 7.5 pmol for each primer and 1.5u TthDNA polymerase. The Stratagene Real Time PCR instrument system has a built in thermal cycler and 4 laser beams directed via fibers optics cables to each of the 96 sample wells. The fluorescent emitted travels each through the cable to the CCD camera detector. Thermal cycler profile consists of 60.0°C for 45 min. RT reaction: 95.0°C for 10 min DNA polymerase activation, 95.0°C for 15 sec denaturation, 60.0°C for 1 min annealing and extension; the main PCR cycle was repeated for 40 cycles. The results were obtained in the form of amplification plot curve.

Histological studies

Samples of nasal tissue were obtained from the inferior turbinate. Paraffin embedding and tissue staining were performed using standard methodologies. All histology slides were examined by two independent histopathologists in a blinded fashion in addition to the authors. A descriptive analysis was performed commenting on the epithelial layer, status of the mucous glands, overall inflammation with the predominant inflammatory cell types and the presence of interstitial fibrosis.

RESULTS

Preliminary results of the questionnaires

Table 1 demonstrates that 52% of HCV patients reported epistaxis (20% mild, 18% moderate and 14% moderate to severe), 16 % reported intermittent nasal obstruction or clear discharge, 18% sneezing on exposure to dust, fumes or irritants and 30% cough. There is a correlation between smoking and cough in HCV group, where 80% of patients who had cough were smokers and 20% non-smokers. On the other hand 0% of control subjects (Table 2) reported epistaxis, 10% intermittent nasal obstruction, 8% intermittent clear nasal discharge, 12% sneezing on exposure to dust, fumes or irritants and 24% cough. There is also a correlation between smoking and cough in the control group, where 75% of subjects with cough were smokers and 25% non-smokers. No correlation between sex or age and

Table 1. Liver function tests, coagulation profile, smoking habit and nasal symptoms in 50 patients with HCV infection, who participated in the preliminary questionnaires. Abbreviations: ALT = Alanine aminotransferase (mean value = 31.22), AST = Aspartate aminotransferase (mean value = 50.78), ALK. Ph. = Alkaline phosphatase (mean value = 73.12), T. Prt. = total protein (mean value = 7.274), Ser. Alb. = Serum albumin (mean value = 4.406), T. Bil. = Total bilirubin (mean value = 0.7578), B.T. = Bleeding time (mean value = 1.984), Proth. = Prothrombin (mean value = 96.36), Fib = Fibrinogen (mean value = 2.378), FDP's = Fibrinogen degradation products (mean value = 15.52), N. Obs. = Nasal obstruction and N. Dis. = Clear nasal discharge. The male to female ratio = 27:23 with mean age = 42.12.

Patient	Age	Sex	ALT	AST	ALK. Ph.	T. Prot.	Ser. Alb.	T. Bil.	B.T.	Prothr.	fib.	FDP's	Sm.	Epistaxis	N. Obs.	N. Dis.	Sn.	Co.
1	24	M	41	28	51	6,8	3,8	0,8	1	100	1	20	+	Mild	–	–	–	+
2	26	F	39	62	62	6,7	3,9	0,9	3	100	2	18	+	–	–	–	–	+
3	25	M	42	59	73	8	4	1	2	98	4	18	+	–	–	–	–	–
4	25	M	36	55	84	7,4	4,1	1	1	98	3	18	+	–	–	+	–	–
5	24	M	28	48	91	7,4	4,6	1	3	98	2,2	17	+	Mild	–	–	+	–
6	32	F	35	49	52	6,7	3,8	1	2	97	3,8	17	–	–	–	–	–	–
7	61	F	29	53	63	7,1	3,9	0,7	2	96	3,9	17	–	–	–	–	–	–
8	62	F	24	56	74	7,4	4	0,8	2	97	3	16	–	Moderate	–	–	+	–
9	54	F	32	48	85	7,2	5,6	0,9	1	98	2,6	20	–	Moderate	–	–	+	–
10	32	F	40	52	90	6,8	6,7	0,8	3	97	2,7	20	–	M-Severe	–	–	+	–
11	48	F	39	50	53	8	7,8	0,7	3	98	3,8	10	–	M-Severe	+	–	–	–
12	21	M	31	41	64	7,5	3,9	0,6	2	99	1,8	11	+	M-Severe	+	–	–	+
13	32	M	30	51	75	7,4	3,8	1	1,8	100	1,9	9	+	Mild	+	+	–	–
14	43	M	22	42	86	6,9	3,7	1	1,6	100	1,8	8	+	–	–	+	+	+
15	54	F	26	53	54	8	3,9	0,5	2,8	100	1,8	12	–	–	–	–	–	–
16	65	F	25	44	65	7	4	0,5	2,9	100	1,8	14	–	Moderate	–	–	–	–
17	76	M	27	54	76	7,1	4	0,4	3	100	1,9	16	+	Mild	–	–	–	+
18	22	M	22	45	87	6,5	4,9	0,3	2	100	1,8	18	+	Moderate	–	–	–	–
19	33	F	39	56	90	7,8	4,6	0,8	0,9	100	2,6	20	+	Moderate	–	–	–	+
20	44	F	37	47	55	7,1	5,2	0,8	2,3	100	2,8	20	+	–	–	–	–	–
21	55	F	30	42	66	8	3,8	0,9	1	92	1,9	20	–	–	–	–	–	–
22	66	F	31	41	78	7,1	3,9	1	2	94	1,9	18	–	–	+	–	–	–
23	71	F	32	45	87	6,5	4	1	1,2	95	2,8	18	–	–	+	–	–	–
24	23	F	40	48	90	7	4	1	1,6	91	3	7	–	–	+	–	–	–
25	34	M	41	40	51	6,9	3,9	1	1,8	90	3	7	+	–	–	–	–	+
26	45	F	41	51	82	7,2	4,8	0,8	2	92	3	8	–	Moderate	–	+	–	–
27	56	M	30	48	85	7,1	5,2	0,7	3	94	4	9	–	M-Severe	–	+	+	–
28	67	M	28	60	74	6,8	6,8	0,5	2	96	2	11	–	M-Severe	–	+	+	–
29	21	M	29	61	69	7,1	4,7	0,8	1	100	2	14	–	–	–	–	–	–
30	32	M	32	62	81	8	3,9	0,2	1	100	2	18	–	–	–	–	–	+
31	43	M	26	48	48	8	3,8	0,7	1	100	1	20	+	–	–	–	–	–
32	54	M	37	61	92	7,3	3,8	0,3	0,6	100	1	14	+	Mild	–	–	–	+
33	65	F	22	40	85	7,5	3,9	0,9	2	100	1	20	+	–	–	–	–	–
34	76	F	26	51	68	7,4	4,2	0,4	2,3	98	1,8	15	–	–	–	–	–	–
35	76	M	25	58	74	6,9	4,1	0,5	3,4	97	1,9	20	–	–	–	–	–	+
36	28	F	32	60	74	6,9	4,6	0,8	0,6	95	2,2	16	+	–	–	–	–	+
37	39	M	41	49	72	8,1	4,7	1	2,1	92	2,1	20	+	Moderate	–	–	–	–
38	41	F	39	50	68	8	3,8	1	2,8	90	2,8	18	–	M-Severe	–	+	–	–
39	56	M	28	56	65	7,5	4,2	1	2,9	98	3,8	17	–	M-Severe	–	–	+	–
40	28	F	19	40	49	7,4	3,9	1	1,8	100	2,1	16	–	Mild	–	–	–	–
41	28	F	18	61	55	7,6	4,3	1	1,7	100	2	14	+	Mild	–	–	–	+
42	24	M	20	62	58	6,8	4,5	0,8	1,6	99	2	15	+	Mild	–	–	–	+
43	24	M	41	49	90	8	4,7	0,8	1,9	99	4	18	+	Moderate	–	–	–	–
44	25	M	32	58	89	7,7	4,7	0,8	2	100	1	15	+	Moderate	–	–	–	–
45	38	M	28	54	72	7,2	4,7	0,8	3	98	1,8	18	+	Mild	–	+	–	–
46	42	M	40	53	68	6,7	4,6	0,9	3	100	2,9	19	–	–	–	–	+	–
47	56	F	29	48	90	7,1	4,5	0,6	3	89	3,2	11	–	–	+	–	–	+
48	28	M	32	51	81	6,9	4,2	0,7	2	47	1,6	12	+	–	+	–	–	+
49	24	M	18	49	85	7,2	3,9	0,4	1	97	2,8	14	+	–	–	–	–	–
50	38	M	30	50	80	7	4	0,09	1,6	99	2,1	15	–	Mild	–	–	–	–

epistaxis could be deduced in HCV group (Table 1). Statistical analysis by Fisher's exact test showed that epistaxis ($p = 0.0001$) but no other nasal symptoms, were more prevalent in the HCV group. Figure 1 compares the percentage of nasal symptoms between control and HCV patients. Statistical analysis by both Fisher's exact test and Chi square test are highly significant for epistaxis but non-significant for other nasal symptoms.

Histopathology of nasal tissue

Figure 2 demonstrates the histopathological changes induced by HCV in the nasal tissue. Interestingly, 12 out of 20 (60%)

Table 2. Liver function tests, coagulation profile, smoking habit and nasal symptoms in 50 control subjects with no HCV infection, who participated in the preliminary questionnaires. Abbreviations: ALT = Alanine aminotransferase (mean value = 35.06), AST = Aspartate aminotransferase (mean value = 51.62), ALK. Ph. = Alkaline phosphatase (mean value = 73.18), T. Prt. = total protein (mean value = 7.216), Ser. Alb. = Serum albumin (mean value = 4.158), T. Bil. = Total bilirubin (mean value = 0.644), B.T. = Bleeding time (mean value = 2.126), Prothr. = Prothrombin (mean value = 95.1), Fib = Fibrinogen (mean value = 2.652), FDP's = Fibrinogen degradation products (mean value = 16.4), Sm. = Smoking, Epi. = Epistaxis, N. Obs. = Nasal obstruction, N. Dis. = Clear nasal discharge, Sn. = Sneezing and Co. = cough. The male to female ratio = 25:25 with mean age = 40.78.

Patient	Age	Sex	ALT	AST	ALK. Ph.	T. Prot.	Ser. Alb.	T. Bil.	B.T.	Prothr.	fib.	FDP's	Sm.	Epi.	N. Obs.	N. Dis.	Sn.	Co.
1	22	M	41	42	91	6,8	3,8	0,8	1,8	98	1	20	+	–	+	–	–	+
2	24	M	32	53	86	8,1	4,2	0,9	3	91	2	19	–	–	–	–	+	–
3	34	M	21	64	57	7,5	3,8	0,6	3	100	3	11	–	–	–	–	–	–
4	56	F	32	64	62	7,5	3,8	1	2,2	92	4	12	+	–	–	–	–	+
5	61	M	30	44	78	8,1	3,4	1	1	90	4	18	+	–	+	–	–	–
6	23	F	49	56	89	7,5	4	1	1	92	2,9	13	–	–	–	–	+	–
7	34	F	28	42	93	8,2	4	1	2,6	93	1,1	20	–	–	–	–	–	–
8	45	M	33	63	50	7,1	4,1	0,5	1	100	3,2	14	+	–	–	–	–	+
9	56	M	47	61	61	6,5	4,2	0,4	3	100	2,8	20	–	–	–	–	–	–
10	67	M	46	62	74	8,1	4,3	0,8	2,8	93	1	17	–	–	–	–	–	–
11	23	F	34	58	55	6,5	4,1	0,3	3	94	4	15	–	–	–	–	–	–
12	28	F	45	41	62	7,1	4	0,2	1,8	94	3,3	16	–	–	–	–	–	–
13	39	F	45	59	83	6,6	3,8	0,6	2,2	95	2	16	+	–	–	–	–	–
14	37	F	30	42	76	6,9	3,9	0,9	3	96	2,7	17	–	–	–	–	–	–
15	42	M	26	57	84	7,1	3,8	0,8	1,9	95	3,4	18	+	–	+	–	–	–
16	56	M	27	45	97	7,5	3,8	0,4	1,7	97	1	20	+	–	–	–	+	+
17	48	M	34	32	58	8,1	4,1	0,5	3	98	3	15	+	–	–	–	–	–
18	49	M	43	64	59	7,9	4,2	0,6	2	96	3,5	20	+	–	–	–	–	–
19	60	M	38	32	65	7,6	5	0,2	2	99	3	20	–	–	–	–	–	–
20	21	M	21	56	70	7,6	4,8	0,8	1,8	90	2	19	–	–	–	–	–	–
21	23	F	49	60	66	6,8	3,8	1	3	97	1,6	18	+	–	–	–	+	–
22	24	F	40	51	81	8,1	3,8	0,3	1	100	3	10	–	–	–	+	–	–
23	28	F	22	48	77	7,5	3,9	0,4	2	98	3,5	11	–	–	–	–	–	+
24	29	M	31	49	52	6,6	4,1	1	2,6	100	3	19	–	–	–	–	–	–
25	60	M	36	49	68	6,9	4,1	0,6	2	91	3,6	12	+	–	–	–	–	–
26	35	M	32	49	83	7,7	3,8	1	1,8	99	3	13	+	–	–	+	–	–
27	40	F	45	58	79	8,1	4,2	0,9	1,9	92	2	17	+	–	–	–	–	+
28	53	M	32	60	84	7,8	3,8	0,8	3	100	2,4	14	+	–	–	–	–	–
29	62	M	31	60	95	6,9	4,3	0,7	3	90	3	16	–	–	+	–	–	–
30	61	F	32	48	50	8,1	4,6	0,2	2,2	93	2,7	15	–	–	–	–	+	–
31	50	F	44	56	61	7,1	3,8	0,6	2,4	94	3	16	–	–	–	–	–	–
32	39	F	43	59	52	7,2	3,8	0,4	1	91	3,3	15	–	–	–	–	–	+
33	28	F	45	52	76	6,4	4,2	0,3	1	95	3	17	–	–	–	–	–	–
34	47	F	41	48	83	6,5	4,1	0,5	1,9	100	2,2	18	–	–	–	–	–	–
35	46	F	33	42	64	7,4	4,7	0,7	1	96	1	20	–	–	–	–	–	–
36	45	M	22	41	97	6,3	4,7	0,2	2,6	92	3	18	+	–	–	–	–	+
37	34	F	21	52	85	6,2	5	0,6	3	97	3,1	19	+	–	–	–	–	–
38	23	M	27	60	78	7,1	5	0,4	1,8	100	3	19	–	–	–	+	–	–
39	22	F	28	48	87	7,2	4,9	0,3	3	98	2,8	20	–	–	–	–	–	–
40	31	F	32	49	69	6,2	3,8	1	2,4	93	2	19	+	–	–	–	+	–
41	60	M	29	40	78	6,3	3,9	1	2	99	2,8	12	–	–	–	–	–	–
42	59	F	36	51	80	7,4	4	0,5	2,5	90	2	17	+	–	–	–	–	+
43	28	M	28	56	99	6,5	4,9	0,7	2,2	94	3,7	13	+	–	–	–	–	–
44	37	M	38	57	50	7,8	4,6	0,7	2,6	91	2	14	–	–	+	–	–	+
45	46	F	43	49	51	6,8	4,8	0,8	2	92	2,9	16	–	–	–	–	–	–
46	55	F	45	52	82	8,1	3,8	0,7	1	100	2	15	+	–	–	–	–	+
47	34	M	32	41	63	6,9	3,9	0,9	1,8	95	2	15	–	–	–	–	–	–
48	43	F	25	60	74	7,1	4	0,7	2,1	93	3,6	20	–	–	–	+	–	–
49	22	F	32	49	85	6,5	4	0,4	1,7	86	2	17	+	–	–	–	–	+
50	50	M	57	50	60	7	4,5	0,6	2	96	2,5	15	–	–	–	–	–	–

HCV positive patients showed epithelial erosion, 19 out of 20 (95%) showed subepithelial non-specific inflammation in the form of mixed chronic inflammatory cellular infiltrate and interstitial fibrosis, as seen in Figure 1-right lane. On the other hand, the control subjects neither had epithelial erosion nor sub-epithelial chronic inflammatory cellular infiltrate or interstitial fibrosis as seen in Figure 2-left lane. None of the 30 studied samples showed glandular hyperplasia (compare left lane representing the control samples with right lane representing HCV positive samples, in Figure 2).

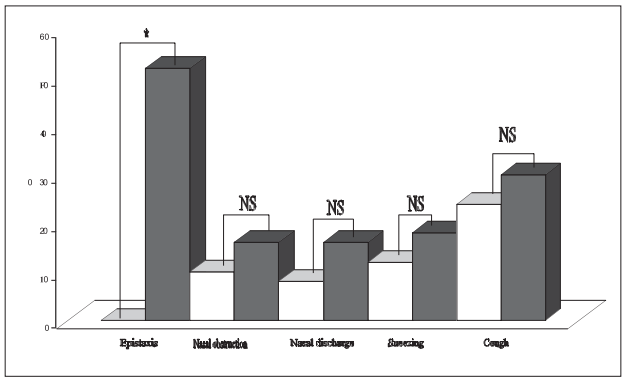

Figure 1. Comparison of the percentage of nasal symptoms between controls (white bars) and HCV patients (black bars). Asterisk indicates $p < 0.001$, while NS indicates $p > 0.05$ by Fisher's exact test and Chi square test. The male to female ratio = 25:25 with mean age = 40.78 for the control subjects, while the male to female ratio = 27:23 with mean age = 42.12 for HCV patients.

Real time-PCR of nasal tissue

As can be seen in Table 3, none of the thirty volunteers who participated in this study, irrespective of their age or sex, tested positive for the presence of the viral antigen in the nasal tissue.

DISCUSSION

HCV seropositive patients may suffer from epistaxis especially in the advanced liver failure stage due to coagulation problems. However, particularly in certain parts of the world where the incidence of seropositive patients is high, we see a considerable number of patients suffering from minor to moderate nasal bleeds requiring several chemical cauterizations. Many of these latter patients have optimal coagulation profile and liver function tests as did the 20 subjects who participated in the current study (data not shown). This led us to hypothesize that potentially viral induced nasal tissue erosion and/or vasculitis could lead to epistaxis. To confirm our clinical observation we first conducted a preliminary study in the form of questionnaires that demonstrated a significantly higher incidence of epistaxis (52%) that required cauterization or nasal packing in HCV patients with normal liver function tests and coagulation profile. Moreover, the non-specific nasal symptoms were higher than the control group but not statistically significant (Fisher's exact test and chi square test).

Table 3. Age, sex, RT-PCR, HCV ab. status, smoking habit and nasal symptoms of the control subjects and HCV infected patients who participated by donating nasal tissue. All thirty subjects had normal ranges of liver function tests and coagulation profile (data not shown). None of the HCV patients received interferon therapy prior to the study. Fisher's exact test is highly significant ($p = 0.0003$) for epistaxis between controls and patients and non significant for other nasal symptoms.

	Controls	Patients	Fisher's Exact Test
Number	10	20	
Sex *Females*	6	12	
Males	4	8	
Mean age	43.2	45.5	
Smoking habit	40%	36%	
HCV-ab	Negative	Positive	
Nasal biopsy PCR	Negative	Negative	
Prick skin test	Negative	Negative	
Epistaxis	0%	70%	$p = 0.0003$
Obstruction	20%	30%	$p > 0.05$
Discharge	10%	15%	$p > 0.05$
Sneezing	10%	20%	$p > 0.05$
Cough	40%	35%	$p > 0.05$

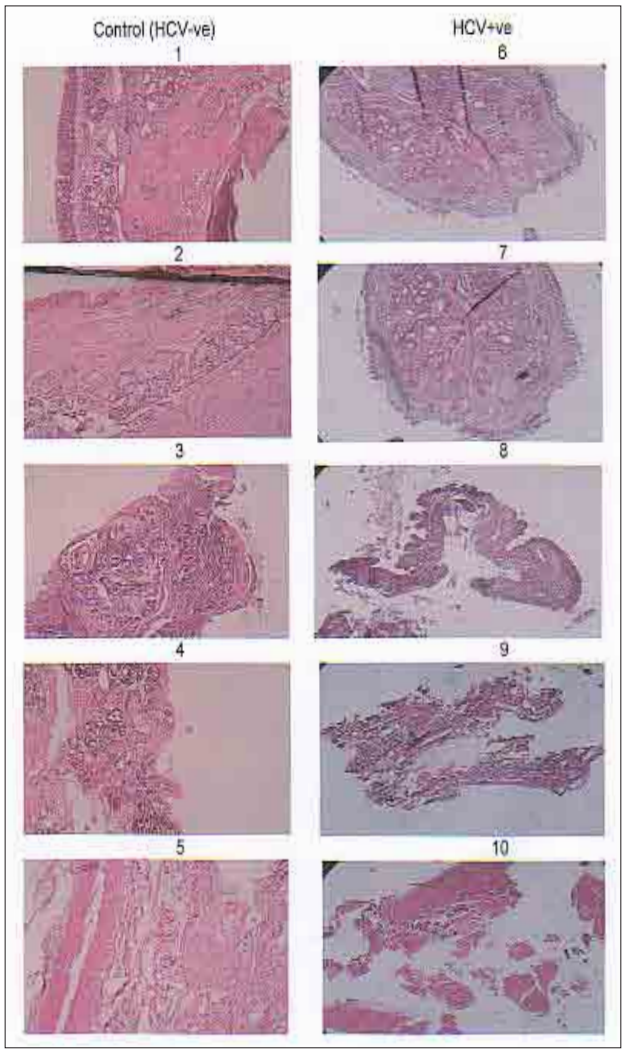

Figure 2. Histological slides of 5 control subject representative of 10 (n = 10) all showing similar results (left lane from 1-5); no epithelial erosion or interstitial fibrosis, and 5 HCV positive subjects, representative of 20 patients (n = 20). Nineteen showing similar results (right lane from 6-10); epithelial erosion and the underlying subepithelial tissue is the seat of variable chronic inflammatory cellular infiltrate (macrophages, plasma cells and mature lymphocytes) with mild to moderate interstitial fibrosis, while only one sample showed normal histology (slide not shown). No sharp evidence of hyperplasia of the mucous glands (1-10).

Next we designed our study and investigated 30 nasal biopsies; 10 from control subjects and 20 from HCV infected patients who had between 2-3 silver nitrate cauterizations for mild to moderate epistaxis in 12 months duration. Interestingly, 60% of HCV positive patient's nasal biopsies showed epithelial erosion, 95% showed subepithelial non-specific inflammation in the form of mixed chronic inflammatory cellular infiltrate and interstitial fibrosis. Taken collectively, there is correlation between the incidence of epistaxis 14 out of 20 (70%) patients and nasal epithelial erosion that may explain at least in part the recurrent mild to moderate epistaxis in HCV positive patients with normal coagulation profile. To this end there are no reports in the medical literature indicating the incidence of mild to moderate epistaxis in HCV infected patients or nasal epithelial erosion by retroviruses. Moreover, the presence of mild to moderate interstitial fibrosis in HCV positive patients correlates well with the chronic nature of the viral infection. The non-significant increase in the incidence of nonspecific rhinitic symptoms in patients with HCV observed in the data from Tables 1-3 may reflect a hyper-responsiveness status of the nasal mucosa due to the epithelial erosion.

No evidence of positive presence of the viral m-RNA by real time-PCR was witnessed. This result suggests that either the viral replication activity was so low in our studied group or actually the nasal tissue does not home the virus. This may render the nasal secretions to be a doubtful source of infection contrary to earlier report that detected the virus in nasal secretions of one out of five patients with high serum viral load[14]. This controversy could be due to the presence of the virus in the tears that drains in the nasal cavity rather than its secretion by nasal tissue.

One possible cause of this histological rhinitis seen in our patients would be either through cryoglobulin deposition, immune complex reaction or viral-induced cytokines inflammation in the level of the airway. The latter is further supported by the implication that airway pulmonary manifestations of chronic hepatitis C virus infection are frequently under-diagnosed [(9)].

In conclusion, our results, although descriptive histologically due to the extreme difficulty of obtaining a large size nasal biopsy, may well characterize the HCV nasal manifestations and may answer our question of whether the mild to moderate epistaxis we see in HCV patients is always a coagulopathy or could be a virus induced rhinopathy. Equally the nasal erosion is worth conducting further studies comparing larger multiracial groups of patients at different stages of liver affection, to further characterize the HCV nasal manifestations and its clinical impact.

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